

B.1. added
conditions which comprises administering to a patient an [anti-inflammatory] anti-inflammatory effective amount of a compound according to claim 1.

B.2.
7/20
7/20
4/1/95
20. (Amended) A method for the treatment and control of inflammatory conditions [in the mammals,] characterized by the topical administration to a patient of an effective dose of a compound according to claim 1.

REMARKS

Claims 1-12 and 17-20 remain in the application; claims 14 and 15 have been canceled; claims 4-12 are withdrawn from consideration; and, claims 18 and 20 have been amended. All of the Examiner's rejections in the final rejection of February 19, 1991, are traversed, and reconsideration is respectfully requested. In the argument which follows, various articles are cited by references to the enclosed articles which are identified by corresponding numbers.

The Examiner's rejection of claims 1, and 17-20 under 35 U.S.C. §103 as being unpatentable over Brattsand et al. (U.S. Patent No. 3,983,233) is respectfully traversed.

The Examiner indicates the data provided are not sufficient to overcome the rejection because:

- (a) The data are not presented in declaration form.
- (b) It is not possible to determine from the data whether they were acquired under the same conditions because

Meier is a foreign language reference which the Examiner cannot comprehend.

- (c) The results presented are not convincing because the Therapeutic Index values for Example 16 of Brattsand et al. and EL-854 are very similar and one of skill in the art would expect the two to have similar activities due to their similar structures.

Ted Tse (1) teaches about the groups essential to anti-inflammatory activity in the basic structure of glucocorticoids. If these groups are present, this pharmacological activity will be preserved. The structure for the claim compounds is in concordance with the basic structure of the glucocorticoids with anti-inflammatory activity (2). Because of this, from a general point of view, the products included in the instant patent application, and all of the compounds structurally related, as those included in the reference patents cited by the Examiner are, show qualitatively common responses.

Structural modifications which preserve the basic structure, as well as the above-mentioned essential groups for anti-inflammatory activity, should be related to quantitative modifications of the same pharmacological responses. So, the goal in the development of new corticoids with anti-inflammatory activity of therapeutic utility, will be to obtain a better quantitative response.

Szefer (2) suggests:

"Although it is feasible to develop synthetic agents that have more potent

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glucocorticoid effect as compared to mineralocorticoid effects, it is not possible to separate the anti-inflammatory effects of glucocorticoids from the metabolic effects. Furthermore, the glucocorticoids significantly suppress hypothalamic-pituitary-adrenocortical (HPA) function".

He also states:

"It must be recognized that methods to increase the anti-inflammatory effects are associated with an increased risk for undesired effects, such as growth suppression, alterations in body habitus, osteoporosis, hypertension, and cataracts. Nevertheless, these agents are beneficial in managing many inflammatory disorders, such as asthma and collagen vascular disease, as well as neoplastic disease, shock, and inhibition of transplant rejection. Methods to optimize effect include the identification of compounds that maximize the ratio of glucocorticoid to mineralocorticoid effects, attempts to deliver the most drug to the relevant site of action, and to define dosing schemes to maintain beneficial effects while minimizing HPA axis suppression".

Clissold et al. (3) notes that:

"A high ratio of local anti-inflammatory to systemic activity appears to be an important indicator relating therapeutic efficacy to systemic tolerability".

In line with this, research has been conducted on corticoids with a structure related to that of the compounds cited by Brattsand et al. (U.S. Patent Nos. 3,983,233 and 3,992,534) which result in a relative improvement in the therapeutic treatment of anti-inflammatory diseases. Among other authors are Brattsand himself (11) and McDonald (10).

From a quantitative point of view, both the general pharmacological activity as well as the ratio between local and

systemic effects, are related essentially to the nature of the substituent radicals and the metabolic pattern of the compounds (11, 12). Relevant differences can be found between compounds containing structurally similar radicals and a structure-activity relationship for the substituent is not known up to today. From the foregoing, it is clear that a higher intrinsic local anti-inflammatory activity and a lower systemic glucocorticoid effect are the desirable properties for a new glucocorticoid intended for topical action, that these properties are related to the nature of the substituent groups and that is not predictable in this relation.

However, the Examiner alleges (Paper No. 6, page 6, second paragraph) that:

"The claimed compounds, compositions and methods of use would have obvious to one of ordinary skill in the art at the time the invention was made because the claimed compounds are structurally related compounds which would be expected to have similar chemical and pharmaceutical properties."

In the patent of Brattsand (A) mentioned by the Examiner, compounds referred in Examples 1, 2, and 3 correspond to the following structures:

Example 1: (Column 3, line 57)

16 α ,17 α -(2'-hydrogen-2'-ethyl) methylene dioxy-9-fluoropregna-1,4-diene-11 β ,21-diol-3,20-dione

Example 2: (Column 9, Table in line 46)

16 α ,17 α -(2;-hydrogen-2 α -n-propyl)methylenedioxy-9-fluoropregna-1,4-diene-11 β ,21-diol-3,20-dione

Example 3: (Column 9, Table in line 46)

16 α ,17 α -(2'-hydrogen-2'-n-butyl)methylene dioxy-9-fluoropregna-1,4-diene-11 β ,21-diol-3,20-dione

So, these three compounds conform a homolog series in respect to radical R₁ of the general formula.

The biological effects of these compounds are summarized by Brattsand in Table 5 of his patent (column 9) and they are reproduced in the following table (a column indicating therapeutics index values, obtained as the quotient between the ED₅₀ values for systemic and topical activities, is included).

Compound	R ₁	Topical Anti-inflammatory activity (Cotton Pellet)	Systemic glucocorticoid activity (Thymus inhib)	Therapeutic Index Systemic ED ₅₀ /Topical ED ₅₀
Ex. 1	Ethyl	35	100	2.86
Ex. 2	n-Propyl	10	> 30	> 3
Ex. 3	n-Butyl	< 3	70	> 23

From the data contained in this table, it can be seen that, in relation to the three compounds of the mentioned homolog series:

- (a) The ED₅₀ values for topical activity are in the range <3 and 35 μ g, that is, they differ by a factor of at least 10.
- (b) The ED₅₀ values for systemic activity are in the range >30 and 100 μ g, that is, they differ by a factor of 3.
- (c) The values for therapeutic index are in the range 2.86 and 23 μ g, that is, they differ by a factor of at least 8.

So, from the data contained in the patent of Brattsand, it is clear that what would have been obvious to one of ordinary skill in the art at the time the invention was made was that structurally related compounds would NOT be expected to have similar pharmaceutical properties.

This conclusion is of application to the compounds included in the instant patent application, as well as those claimed by Brattsand in the mentioned patent.

The Examiner specifically has mentioned compound 16 presented in Table 4, column 5, of Brattsand (A), indicating the structural similarity with the compound claimed in the instant application in which R₁ is butyl and R₂ is acetyl. The present patent application does not cover experimental data on the pharmacological activity of said compound; however, the data are available in proprietary files (compound EL-854). The comparison of these data with compound 16 of Brattsand is indicated below:

Compound	Topical anti-inflammatory activity (Cotton Pellet)	Systemic glucocorticoid activity (Thymus inhib)	Therapeutic Index Systemic ED50/ Topical ED50
Ex. 16 U.S. Patent No. 3,983,233	< 3	30	> 10
EL-854	8.6	147	17.1

From the data contained in this table, it is derived that:

- (a) The ED₅₀ values for topical activity differ by a factor of at least 3.

(b) The ED_{50} values for systemic activity differ by a factor of 5.

Applicants are prepared to present the foregoing data in declaration form.

The Applicants consider that these results do not support the assessment of the pharmacological activities of both compounds are similar, especially if the scope of minimize systemic glucocorticoid effect on claim 18 is taken in consideration.

Neither the compound indicated by the Examiner (the above-mentioned EL-854) nor any other of the compounds claimed in the instant application are specifically mentioned in the patent of Brattsand et al.

Moreover, the compounds claimed in this application show pharmacological properties of patentable utility because there are differences not obvious at the time the invention was made to a person having ordinary skill in the art between the subject matter sought to be patented and the prior art.

This assessment is derived from comparison of the values of anti-inflammatory potency of the compounds from the instant invention and the corresponding values of those included in the patent of McDonald (U.S. Patent No. 4,835,145) Tables II and III (10). The results on relative potency of the compounds included in the instant invention are derived from the quotient ED_{50} (22 R,S)-compound (column "topical anti-inflammatory activity" on table III from the instant invention).

The results are shown in the following table:

Patent	Compound	Relative Topical anti-inflammatory potency (Budesonide = 1)
U.S. Patent No. 3,983,233 (Brattsand)	Ex. 22 (More potent of all the compounds)	1.49*
U.S. Patent No. 4,835,145 (McDonald)	2 e 2 f 2 g 2 i	3.03 4.86 1.80 5.90
U.S. Patent Application Serial No. 578,942 (Calatayud)	7 10 13	7.54 2.73 36.35

*=Table III of U.S. Patent No. 4,835,145

The pharmacological data of the compounds of the instant invention are compared with those included in the patent of McDonald because:

- (a) The patent of McDonald is later than that of Brattsand and represents the latest teaching of the relevant art.
- (b) Data on pharmacological activity mentioned by McDonald were acquired by the same test method employed by the instant Applicants [Method of Meier et al. (8)].
- (c) Budesonide is used as reference compound by McDonald and the Applicants. In this way, possible differences in experimental conditions are overcome.

From this data is derived that the compounds claimed in the present patent application show a better anti-inflammatory potency than those included in the patents of reference.

This better response can be related to:

- (a) Bulkiness of the substituents, because bulk differences in R_1 can provide better responses (12).

(b) A better topical anti-inflammatory response.

Moreover, it is clear from the data presented in Table III of the specification that the compounds included in this application possess a better relation between the topical anti-inflammatory activity and systemic effects. This can be due to metabolic patterns of the compounds of the instant invention. Comparative studies on inactivation of Ciclesonide* by hepatic oxigenases show that the systemic action of Ciclesonide is lower than that action of Budesonide by p.o. and s.c. routes of administration. (13)

From the foregoing discussion, it is clear that:

- (a) Though they are structurally related, the compounds claimed in the instant patent application are not specifically disclosed or suggested by the references.
- (b) They show higher topical anti-inflammatory activity (inhibition of the growth of the granuloma) and lower systemic effects (reduction of the thymus weight), and more advantageous hepatic metabolism; and, therefore, a better therapeutic index than the steroids of the prior art.

As a result, the use of the compounds claimed in the present application are not a matter of preference depending on factors not related to pharmaceutical properties, but represents an unexpected therapeutic improvement with regard to other steroids; and, therefore, could be considered patentable.

*Ciclesonide: Name given to the Compound No. 7 by the INN of the WHO.

The Examiner's rejection of claims 1-3, and 17-20 under 35 U.S.C. §103 as being unpatentable over Brattsand et al. (U.S. Patent No. 3,983,233) as applied above in view of Brattsand et al. (U.S. Patent No. 3,992,534) is also traversed.

In response to the last paragraph of page 6 to page 7 of the Office Action (Paper No. 6) regarding epimers claimed in the present invention, and their structural similarity to the Brattsand et al. compounds (A) and (B), Applicants note:

- (a) Applicants feel that the differences indicated above between the compounds of claim 1 of the instant application and the reference patents cited by the Examiner are also valid in the case of the isolated epimers of these compounds.
- (b) The products included in the instant patent application, as well as those mentioned by Brattsand et al., contain a chiral center in C-22 and, consequently, they can exist as mixtures of epimers. Nevertheless, none of the epimers claimed in the present application are specifically included in or suggested by Brattsand et al. (U.S. Patent No. 3,992,534).
- (c) Brattsand et al. (U.S. Patent No. 3,992,534) specifically mentions the compounds of their Examples 1, 3, 5, 7, 8, and 12 as preferred, based upon the characteristics of component B.

The pharmacological data of these compounds and their epimers preferred by Brattsand Table 3, columns 10 and

11, are compared with the data corresponding to instant compounds (Table III of our patent application).

Compound	µg/animal to obtain 50% inhibition of		Therapeutic Index ED50 Thymus/ ED50 Granuloma
	Granuloma growth	Thymus weight	
Ex. 1* A + B A B	120 270 30	270 115 50	2.25 0.42 1.66
Ex. 8* A + B A B	10 25 3	> 30 > 30 17	3 1.2 5.6
Ex. 7* A + B A B	no data 15 10	no data 12 6	- 0.8 0.6
Ex. 8* A + B A B	5 6 4	10 13 10	2 2.1 2.5
Ex. 12* A + B A B	100 125 40	80 125 70	0.8 1 1.75
Ex. 7** 22 R,S	21.7	614.7	28.3
Ex. 8** 22 S	20.5	608	29.6
Ex. 9** 22 R	25.4	667.1	26.2
Ex. 10** 22 R,S	59.9	583.2	9.7
Ex. 11** 22 S	43	555.3	12.9
Ex. 12** 22 R	74.7	592.2	7.9
Ex. 13** 22 R,S	4.5	54	12
Ex. 14** 22 S	3.6	49	13.6
Ex. 15** 22 R	5.2	56.3	10.8

*=Brattsand (B) (U.S. Patent No. 3,992,534

**=U.S. Patent Application No. 578,942

From these data, it is clear that in all the cases, the therapeutic index of the compounds claimed in the instant application and their epimers are more favorable than those shown by the compounds mentioned by Brattsand et al. and component B of the aforementioned Brattsand compounds.

From the foregoing discussion, we can consider that:

- (a) Though they are broadly and structurally related, the epimers claimed in the present application are neither specifically mentioned nor in any way suggested by or obvious from the teaching of the cited references.
- (b) They show an unexpected, better relationship between local anti-inflammatory activity and systemic effects than the epimers claimed in the reference patent. So a better therapeutic index than that of the steroids of the prior art is clear. This means a significant therapeutic improvement in relation with other glucocorticoids.

The Examiner rejected claims 18 and 20 under 35 U.S.C. §§101 and 112, first paragraph, because no evidence has been presented that the claimed method would possess utility in humans. Proof of human utility is required unless it can be shown that one of ordinary skill in the art would accept the utility as obviously valid.

It is Applicants' position that the human utility of the compounds of the instant invention could be considered obvious to one of ordinary skill in the art since the compounds of the instant invention have a chemical structure which correspondence to corticoids; and, according to the ordinary skill in the art, it is well known that the human utility of the corticoids, is related with their anti-inflammatory activity. The following literature support is cited (Numbers in parenthesis correspond to number of attached article).

- ✓
1. Ted Tse (1), pp. 334:

"Since the 1950s, corticosteroids aerosols have proved useful in the treatment of asthma. Although their precise mechanism of action is not know, these topical agents have beneficial anti-inflammatory and decongestive effects on the bronchial tree in both the allergic and non-allergic forms of this disease".

2. Ted Tse (1), pp. 336, line 12:

"In theory, the most beneficial effect of steroids in the treatment of asthma are their anti-inflammatory and decongestive effects on bronchial mucous membranes."

3. S. J. Szeffler (2), pp. 355, line 1:

"The primary applications of corticosteroids therapy is directed toward the anti-inflammatory effects of these compounds."

4. Clissold et al. (3) pp. 489, line 28:

"A high ratio of local anti-inflammatory to systemic activity appears to be an important indicator relating therapeutic efficacy to systemic tolerability."

5. Szelengi (4), pp. 30, line 11:

"That corticosteroids are the most effective drugs currently available for the long-term management of asthma". "Since they suppress virtually every stage of the inflammatory response in asthmatic airways steroid probably..."

6. Bardin and Holgate (5), pp. 108:

"Treatment of inflammation in asthma. Corticosteroids have been used to treat asthma for more than 30 years are the mainstay of medication in many asthmatics. This drug does inhibit the allergen-induced LAR and acquired increases in BHR probably by suppressing components of inflammation."

7. Kelly and Murphy (6), pp. 72, line 15:

"The basic molecular genetics, cellular mechanisms, and biologic effects of the corticosteroids relevant to asthma therapy have recently been reviewed. The pharmacologic effects that may be of benefit in acute, sever asthma include anti-inflammatory activity, inhibition of mucous secretion, potentiation of beta-adrenergics, decreased microvascular permeability and reduction of alveolar-arterial oxygen tension gradient and venous admixture effects. Of these, corticosteroids myriad effects on the inflammatory process are the most important and may explain some of the inconsistencies found in the literature."

8. Streeten and Phil (7), pp. 994:

"General actions of corticosteroids. Anti-inflammatory and Anti-Allergic Actions. Steroids nonspecifically inhibit the inflammatory effects of many noxious agents, including microorganisms, chemical or thermal irritants, trauma and allergens."

On the other hand, the corticosteroid of the instant invention are physiologically active compounds, possessing anti-inflammatory activity according with the data included in the specification (Table III); but, this activity is higher than well-known reference compounds: Budesonide, Triamcinolone Acetonide, and Flunisolide.

Table III (Included in the declaration form)

Local pharmacologic activity and systemic glucocorticoid effects expressed as ED50 μ g/pellet

Compound	Epimer	Topical Anti-inflammatory Activity (Cotton Pellet)	Systemic Glucocorticoid Activity (Thymus Inhib)	Therapeutic Index Systemic ED50/ Topical ED50	Therapeutic Index with Respect to Budesonide
7	22 R,S	21.7 (17 - 27.7)	614.7 (279.6 - 1351)	28.3	26
8	22 S	20.5 (16.9 - 25.6)	608 (359.3 - 1228.3)	29.6	27.2
9	22 R	25.4 (18.2 - 31.1)	667.1 (321.4 - 1489.2)	26.2	24.5
10	22 R,S	59.9 (59.3 - 60.3)	583.2 (236.2 - 1440)	9.7	8.9
11	22 S	43 (38.4 - 58)	553.3 (296.3 - 1387.3)	12.9	11.5
12	22 R	74.7 (65.1 - 83.3)	592.2 (265.1 - 1342.9)	7.9	7.2
13	22 R,S	4.5 (3.7 - 5.5)	54 (33 - 83.3)	12	11
14	22 S	3.6 (3 - 4.5)	49 (30.7 - 76.2)	13.6	15
15	22 R	5.2 (3.6 - 6)	56.3 (29.8 - 88.3)	10.8	9.9
Budesonide	22 R,S	163.6 (125.1 - 213.9)	178.6 (81.3 - 392.6)	1.09	1
Triamcinolone		220.7 (198.1 - 245.7)	156.4 (144.7 - 169)	0.7	0.6
Flunisolide		351.6 (268.8 - 459.9)	156 (133.3 - 224.8)	0.44	0.4

The experimental procedure used has been described by Meier et al. (8)", and this test has been used by many authors to evaluate the anti-inflammatory activity of new compounds. Freeman et al. (9), pp. 573, line 14, states: "The original test of Meier appears to have the advantage that it provides a method of distinguishing steroidal type drugs from their non-steroidal counterparts". Also, McDonald (10) acknowledges: "The U.S. Patent No. 4,835,145 example described the use of the Meier test to evaluate the anti-inflammatory activity of different new corticoids." We can thus conclude that to one of ordinary skill in the art, the cotton pellets induced granuloma used by Meier et al., could be considered valid to study the local anti-inflammatory activity and also systemics effects in the form of retrogression of thymus and inhibition of body weight.

The anti-inflammatory potencies found in the screening models as that used by Meier et al., intended for evaluation of the topical anti-inflammatory activity thus seem to also be a rather good prediction of the anti-asthmatic activity in humans.

In this way, we also rely on U.S. Patent No. 4,835,145, in which there are several claims (claim nos. 3, 6, 9, 12, and 15) related to a method of treating inflammatory conditions, on the basis to a topical anti-inflammatory efficacy derived from the ability to inhibit cotton pellet induced granuloma by the method described by Meier et al.

" We annex hereto a copy of the original publication in German and English translation.

Since the compounds of the instant invention are corticoids, the utility of these drugs is based on its anti-inflammatory activity, which anti-inflammatory activity has been demonstrated in the specification using a valid method for this purpose, we conclude that one of ordinary skill in the art would accept the utility of the compounds described in the invention as obviously valid for the use in humans.

The Examiner has rejected claims 17, 18, and 20 under 35 U.S.C. §112, second paragraph.

As to claim 17, the Examiner argues that

"This claim is redundant in that it is not distinct from claim 1, from which it depends."

The terms "drug" and "compound" in claim 17, used by the inventors, are in the sense of Churchill's Medical Dictionary, Ed. 1989.

Compound 1A: "A substance composed by different elements."
(Churchill's Medical Dictionary, pp. 404, Ed. 1989)

Drug: "A medicinal chemical compound that is used for the treatment of diseases for the prevention of pathologic states, or for the diagnosis of diverse conditions in man and animals." (Churchill's Medical Dictionary, pp. 564, Ed. 1989)

As to claim 18, the Examiner also argues that:

"Claim 18 is open-ended. It is not clear to what or whom the method is applied."

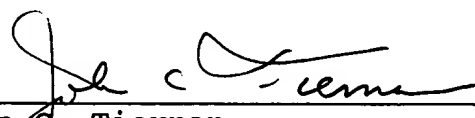
As to claim 20, the Examiner states:

"Claim 20 lacks antecedent basis in the specifications because mammals are not described in the specification."

Both claims have been amended to overcome the Examiner's objections.

It is respectfully submitted that the foregoing amendments should be entered to place the case in better condition for approval, and that the foregoing argument clearly show that Applicants' claims are patentable over all of the references and combinations of references being relied upon by the Examiner. In view of the foregoing, withdrawal of the Examiner's rejection, allowance of the claims, and passage of the case to issue are respectfully solicited.

Respectfully submitted,

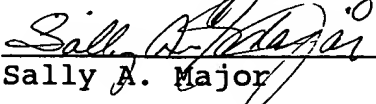


John C. Tiernan
Reg. No. 21,078

FAY, SHARPE, BEALL, FAGAN,
MINNICH & McKEE
1100 Superior Avenue; Suite 700
Cleveland, Ohio 44114-2518
(216) 861-5582

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Sally A. Major